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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 79N–0113; DESI 2847]

Pediatric Parenteral Multivitamin Products; Drug Efficacy Study Implementation; Announcement of Marketing Conditions

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that pediatric parenteral multivitamin drug products that are formulated as set forth in this document are effective for treating certain vitamin deficiencies. FDA is further announcing the conditions for the approval and marketing of the drug products for the indications for which they are now regarded as effective.

DATES: Supplements to the conditionally approved new drug application (NDA) must be submitted by [*insert date 60 days after date of publication in the* **Federal Register**].

ADDRESSES: Communication in response to this notice should be identified with the reference number DESI 2847 and directed to the attention of the appropriate office named below.

Supplements to the conditionally approved NDA (identify with NDA number): Division of Metabolic and Endocrine Drug Products (HFD–510), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Original abbreviated new drug applications (ANDA's): Office of Generic Drugs (HFD–600), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

Requests for opinion of the applicability of this notice to a specific product: Division of Prescription Drug Compliance and Surveillance (HFD–330), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

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assumptions applied by the AMA to correlate the established dietary allowances of the essential vitamins to the parenteral administration of vitamins to patients in various disease states required that clinical trials be conducted to evaluate the guideline formulations.

FDA accepted the AMA guidelines with minor reservations and, subsequently, in a **Federal Register** notice published July 13, 1979 (44 FR 40933), amended the terms of the December 1972 paragraph XIV temporary exemption to require conditional approval of an NDA or supplemental NDA within specific time frames as a condition for the continued marketing of a parenteral multivitamin drug product. The agency agreed not to initiate regulatory proceedings against these products under the following requirements: (1) Reformulation in accord with the AMA guidelines as to the number and quantities of vitamins in the formulation; (2) an outline of proposed studies along the lines set forth in the AMA report, to evaluate the stability and biological availability of the reformulated preparations; and (3) a plan or protocol for clinical effectiveness studies in accord with the AMA guidelines. A reformulated product could be marketed in place of the previous formulation after agency review and conditional approval of the submission. This procedure allowed continued marketing of parenteral multivitamins while clinical testing and evaluation of the AMA guideline formulations were being carried out.

After evaluating available data, FDA classified the AMA guideline adult formulations as effective in the **Federal Register** of September 17, 1984 (49 FR 36446). That notice also revoked the paragraph XIV exemption of all products listed in the notice, including the following pediatric product conditionally approved under the terms of the July 13, 1979, notice (in accordance with current labeling practice, amounts previously listed in United States Pharmacopeia units have been converted to weights):

NDA 18–920; M.V.I. Pediatric (lyophilized), each vial containing vitamin A (retinol) 0.7 milligrams (mg)/vial, vitamin D (ergocalciferol) 10 micrograms (µg)/vial, vitamin E (dl-alpha tocopherol acetate) 7 mg/vial, vitamin C (ascorbic acid) 80 mg/vial, folic acid 140 µg/vial, niacin (niacinamide) 17.0 mg/vial, vitamin B_2 (riboflavin-5′-phosphate sodium) 1.4 mg/vial, vitamin B_1

(thiamine hydrochloride) 1.2 mg/vial, vitamin B_6 (pyridoxine hydrochloride) 1.0 mg/vial, vitamin B_{12} (cyanocobalamin) 1 μg/vial, dexpanthenol (d-pantothenyl alcohol) 5.0 mg/vial, biotin 20 μg/vial, vitamin K (phytonadione) 200 μg/vial; Astra Zeneca, 50 Otis St., Westborough, MA 01581 (formerly held by Armour Pharmaceutical Co., P.O. Box 511, Kankakee, IL 60901).

The September 17, 1984, notice stated that further evaluation of pediatric parenteral multivitamin formulations containing vitamin E was required. The notice went on to state that until the time that such evaluation was completed, pediatric multivitamin products could be marketed only under the terms and conditions of the July 13, 1979, **Federal Register** notice.

The effectiveness of the AMA guideline pediatric formulations was considered by an AMA–FDA committee in the Workshop on Multivitamin Preparations for Parenteral Use on August 21, 1985, and by FDA's Endocrinologic and Metabolic Drugs Advisory Committee on March 3 and 4, 1986. Based on a review of the committees' recommendations and other available material, the Director of the Center for Drug Evaluation and Research has determined that the 1975 AMA guideline pediatric formulations are effective multivitamin preparations.

It should be noted, however, that although the intravenous preparation is properly formulated in composition and dosage amount of essential vitamins, it supplies inadequate amounts of vitamin A, particularly to low birth weight infants. In addition, the issue of whether the solubilizers used in pediatric preparations contribute to toxicity remains unresolved. Further study of the pediatric formulations is needed to determine a vehicle for administration of multivitamins to low birth weight infants that will provide adequate amounts of vitamin A and avoid possible toxicity associated with the use of solubilizers employed in pediatric preparations. Future approval of a more appropriate formulation for low birth weight infants may restrict the labeling of the current formulation to use in infants weighing more than 3 kilograms (kg).

The continuing exemption announced in the September 17, 1984, notice for pediatric parenteral multivitamin products is hereby revoked. These products are regarded as new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). Therefore, a

fully approved NDA is required to market them. M.V.I. Pediatric (NDA 18–920) received conditional approval under the terms of the July 13, 1979, notice. A supplemental NDA is now required for M.V.I. Pediatric to revise the labeling and to update its conditionally approved NDA.

In addition to the product specifically named above, this notice applies to any product that is not the subject of an approved application and is identical or, under 21 CFR 310.6, is related or similar to M.V.I. Pediatric. It is the responsibility of all drug manufacturers and distributors to review this notice to determine whether it covers any drug product that they manufacture or distribute. Any person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division of Prescription Drug Compliance and Surveillance (address above).

II. Conditions for Approval and Continued Marketing of Formulations Evaluated as Effective

A. Effectiveness Classification

FDA has reviewed all available evidence and concludes that pediatric parenteral drug products formulated as listed below are effective for the applicable indication set forth in the labeling conditions below.

B. Conditions for Approval and Marketing

FDA is prepared to approve ANDA's and supplements to the conditionally approved NDA named above under conditions described here.

1. Form of Drug

(a) *Intravenous multivitamin preparations.* The preparation is an aqueous solution or lyophilized powder suitable for reconstitution and/or secondary dilution prior to intravenous infusion and contains the specified amounts of the following individual vitamins, either as the moiety listed below or as the chemically equivalent salt or ester.

(i) *Pediatric formulation* (intended for infants and children under age 11)[1]

Ingredient	Amount per Unit Dose
Fat-Soluble Vitamins	
A (retinol)	0.7 mg
D (ergocalciferol or cholecalciferol)	10 μg
E (alpha-tocopherol)	7 mg
K_1 (phytonadione)	200 μg
Water-Soluble Vitamins	
C (ascorbic acid)	80 mg
Folic acid	140 μg
Niacin	17 mg
B_2 (riboflavin)	1.4 mg
B_1 (thiamine)	1.2 mg
B_6 (pyridoxine)	1.0 mg
B_{12} (cyanocobalamin)	1.0 μg
Pantothenic acid	5.0 mg
Biotin	20.0 μg

[1]For infants weighing less than 1 kg the daily dose is 30 percent of the indicated formulation. Do not exceed this daily dose. For infants weighing 1 to 3 kg the daily dose is 65 percent of the indicated formulation.

(b) *Intramuscular multivitamin preparations.* The preparation is a sterile solution suitable for intramuscular injection.

(i) *Pediatric formulation.* The vitamin composition of the pediatric intramuscular formulation shall be that of the pediatric intravenous preparation named above without the fat-soluble vitamins.

2. Labeling Conditions

(a) The label bears the statement ''Caution: Federal law prohibits dispensing without prescription.''

(b) The drug is labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The indication is as follows:

(i) *Intravenous Pediatric Multivitamin Preparations.* This formulation is indicated as a daily multivitamin maintenance dosage for infants and children up to 11 years of age receiving parenteral nutrition.

It is also indicated in other situations where administration by the intravenous route is required. Such situations include surgery, extensive burns, fractures and other trauma, severe infectious diseases, and comatose states, which may provoke a ''stress'' situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients.

The physician should not await the development of clinical signs of vitamin deficiency before initiating vitamin therapy.

This product (administered in intravenous fluids under proper dilution) contributes intake of these necessary vitamins toward maintaining the body's normal resistance and repair processes.

Patients with multiple vitamin deficiencies or with markedly increased requirements may be given multiples of the daily dosage for two or more days as indicated by the clinical status.

(ii) *Intramuscular Pediatric Multivitamin Preparations.* This product is indicated for infants and children up to ll years of age for conditions in which: (1) Intake or absorption of the water-soluble vitamins is inadequate and oral intake must be supplemented; or (2) there is a known or suspected serious depletion of the water-soluble vitamins, and immediate treatment by the intramuscular route is advisable.

Conditions that may require parenteral administration of water-soluble vitamins may include disorders that can affect oral intake, gastrointestinal absorption, or utilization. Such conditions include comatose states, persistent vomiting, prolonged fever, severe infectious diseases, major surgery, extensive burns, fractures and other traumas, diarrhea, achlorhydria, or liver disease.

The physician should not await the development of clinical signs of vitamin deficiency before initiating therapy because there are few specific or pathognomonic signs of early vitamin deficiencies.

(c) CONTRAINDICATIONS: Known hypersensitivity to any of the vitamins or excipients in this product or a preexisting hypervitaminosis.

Allergic reaction has been known to occur following intravenous administration of thiamine and vitamin K. The formulation is contraindicated prior to blood sampling for detection of megaloblastic anemia, as the folic acid and the cyanocobalamin in the vitamin solution can mask serum deficits.

(d) PRECAUTIONS: (The following paragraph should appear in bold type)

Caution should be exercised when administering this multivitamin formulation to patients on warfarin sodium-type anticoagulant therapy. In such patients, periodic monitoring of prothrombin time is essential in determining the appropriate dosage of anticoagulant therapy.

Adequate blood levels of vitamin E are achieved when this product is given to infants at the recommended dosage. Larger doses or supplementation with oral or parenteral vitamin E are not recommended because elevated blood levels of vitamin E may result.

Studies have shown that vitamin A may adhere to plastic, resulting in inadequate vitamin A administration in the doses recommended with this product. Additional vitamin A supplementation may be required, especially in low birth weight infants.

3. Marketing Status

(a) Marketing of the drug product that is now the subject of a conditionally approved NDA may be continued provided that on or before [*insert date 60 days after date of publication in the* **Federal Register**], the holder of the application has submitted: (i) A supplement for revised labeling necessary to be in accord with the labeling conditions described in this notice, and complete container labeling if current container labeling has not been submitted; and (ii) a supplement to provide updated information with respect to the composition, manufacture, and specifications of the drug substance and the drug product as described in 21 CFR 314.50(d)(1)(i) and (d)(1)(ii). FDA will evaluate the submitted material and, if the material is adequate, will grant full approval to the conditionally approved NDA.

(b) Approval of an ANDA must be obtained in accordance with section 505(j) of the act (21 U.S.C. 355(j)) before marketing such products. Marketing prior to approval of an ANDA will subject such products, and those persons who caused the products to be marketed, to regulatory action.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505 (21 U.S.C. 352, 355)) and under authority delegated to the Director, Center for Drug Evaluation and Research (21 CFR 5.70).

Dated: January 4, 2000

Janet Woodcock
Director
Center for Drug Evaluation and Research

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